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Draft Guidance For Industry

STABILITY TESTING OF NEW ANIMAL DRUG SUBSTANCES AND PRODUCTS

DRAFT GUIDANCE FOR COMMENT

This draft guidance discusses the stability testing requirements for an application for marketing permission Registration Application within the European Union, Japan, and the USA. It does not necessarily seek to cover the testing that may be required for registration in or export to other areas of the world. The intent is to provide a general indication of the stability testing recommendations while allowing sufficient flexibility to cover the variety of different scientific situations and material characteristics being evaluated.

This guidance represents current thinking and does not create or confer any rights for or on any person and does not operate to bind FDA or the public. Alternative approaches maybe used if they satisfy applicable requirements.

Comments and suggestions regarding the document should be submitted to Docket No. 97N- [insert number when assigned]. For questions regarding this draft document, contact William G. Marnane, Center for Veterinary Medicine, (HFV- 140), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-594-0678, E-mail: wmarnane@fda.gov.

U.S. Department of Health and Human Services
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STABILITY TESTING OF NEW ANIMAL DRUG SUBSTANCES AND PRODUCTS

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STABILITY TESTING OF NEW ANIMAL DRUG SUBSTANCES AND PRODUCTS

Recommended for Consultation
at Step 4 of the VICH Process
on 27 February 1998
by the VICH Steering Committee

Note

Attachment I (which is an annex to the minutes of the VICH Quality WG meeting of September 30, 1997) provides a consensus interpretation intending to clarify two specific points. This annex is part of the guidance.

THIS GUIDANCE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP ON THE BASIS OF THE I CH GUIDANCE ON THE SAME SUBJECT AND IS SUBJECT TO CONSULTATION BY THE PARTIES , IN ACCORDANCE WITH THE VI CH PROCESS . AT STEP 7 OF THE PROCESS THE FINAL DRAFT WILL BE RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN AND USA .

STABILITY TESTING OF NEW ANIMAL DRUG SUBSTANCES AND PRODUCTS

Endorsed by the VICH Steering Committee at Step 3 of the VICH Process

27 February 1998

PREAMBLE

The following guidance sets out information on stability testing for a Registration Application within the three areas of the EC, Japan, and the USA. It does not seek necessarily to cover the testing that may be needed for registration in or export to other areas of the world.

The guidance seeks to exemplify the core stability data package needed for new drug substances and products. It is not always necessary to follow this when there are scientifically justifiable reasons for using alternative approaches.

The guidance provides a general indication on the requirements for stability testing, but leaves sufficient flexibility to encompass the variety of different practical situations required for specific scientific situations and characteristics of the materials being evaluated.

The guidance that information on stability generated in any one of the three areas of the EC, Japan, and the USA would be mutually acceptable in both of the other two areas has been established, provided it conforms to the elements of this guidance and the labeling is in accord with national/regional requirements.

Details of the specific requirements for sampling, test requirements for particular dosage forms/packaging, etc., are not covered in this guidance.

OBJECTIVE

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and enables recommended storage conditions, re-test periods, and shelf lives to be established. Since guidance is not legally binding, an applicant may submit justification for an alternative approach.

SCOPE

The guidance primarily addresses the information that should be submitted in Registration Applications for new molecular entities and associated drug products. The information for biological products and pre-mix products for medicated feedingstuffs will be the subject of separate guidelines.

This guidance does not currently seek to cover the information required for abbreviated or abridged applications, variations, clinical trial applications, etc.

The choice of test conditions defined in this guidance is based on an analysis of the effects of climatic conditions in the three areas of the EC, Japan, and the USA. The mean kinetic temperature in any region of the world can be derived from climatic data (Grimm, W., *Drugs* Made ***in Germany, 28:196-202, 1985,*** and 29:39-47, 1986).

DRUG SUBSTANCE

General

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

Stress Testing

Stress testing helps to determine the intrinsic stability of the molecule by establishing degradation pathways in order to identify the likely degradation products and to validate the stability indicating power of the analytical procedures used.

Formal Studies

Primary stability studies are intended to show that the drug substance will remain within specification during the re-test period if stored under recommended storage conditions.

Selection of Batches

Stability information from accelerated and long term testing is to be provided on at least three batches. The long term testing should cover a minimum of 12 months duration on at least three batches at the time of submission.

The batches manufactured to a minimum of pilot plant scale should be by the same synthetic route and use a method of manufacture and procedure that simulates the final process to be used on a manufacturing scale.

The overall quality of the batches of drug substance placed on stability should be representative of both the quality of the material used in pre-clinical and clinical studies and the quality of material to be made on a manufacturing scale.

Supporting information may be provided using stability data on batches of drug substance made on a laboratory scale.

The first three production batches of drug substance manufactured post approval, if not submitted in the original Registration Application, should be placed on long term stability studies using the same stability protocol as in the approved drug application.

Test Procedures and Test Criteria

The testing should cover those features susceptible to change during storage and likely to influence quality, safety, and/or efficacy. Stability information should cover as necessary the physical, chemical, and microbiological test characteristics. Validated stability-indicating testing methods should be applied. The need for extent of replication will depend on the results of validation studies.

Specification

Limits of acceptability should be derived from the profile of the material as used in the pre-clinical and clinical batches. It should to include individual and total upper limits for impurities and degradation products, the justification for which should be influenced by the levels observed in material used in pre-clinical studies and clinical trials.

Storage Conditions

The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use. Application of the same storage conditions as applied to the drug product will facilitate comparative review and assessment. Other storage conditions are allowable if justified. In particular, temperature sensitive drug substances should be stored under an alternative, lower temperature condition which will then become the designated long term testing storage temperature. The six months accelerated testing should then be carried out at a temperature at least 15°C above this designated long term storage temperature (together with the appropriate relative humidity conditions for that temperature). The designated long term testing conditions will be reflected in the labeling and re-test date.

	Conditions	Minimum time period at submission
Long term testing	25°C ± 2°C/60% RH ±5%	12 months
Accelerated testing	400C ± 2°C/75% **RH** ±5%	**6** months

Where 'significant change' occurs during six months storage under conditions of accelerated testing at 40"C ± 2°C/75 percent RH ± 5 percent, additional testing at an intermediate condition (such as 30°C ±2 °C/60 percent RH ± 5 percent) should be conducted for drug substances to be used in the manufacture of dosage forms tested long term at 25 °C/60 percent RH and this information included in the Registration Application. The initial Registration Application should include a minimum of 6 months data from a 12 months study. 'Significant change' at 40°C/75 percent RH or 30°C/60 percent RH is defined as failure to meet the specification.

The long term testing should be continued for a sufficient period of time beyond 12 months to cover all appropriate re-test periods, and the further accumulated data can be submitted to the Authorities during the assessment period of the Registration Application.

The data (from accelerated testing or from testing at an intermediate condition) may be used to evaluate the impact of short term excursions outside the label storage conditions such as might occur during shipping.

Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the drug substance. Testing under the defined long term conditions should normally be every three months over the first year, every six months over the second year, and then annually.

Packaging/Containers

The containers to be used in the long term, real time stability evaluation should be the same as or simulate the actual packaging used for storage and distribution.

Evaluation

The design of the stability study is to establish, based on testing a minimum of three batches of the drug substance and evaluating the stability information (covering as necessary the physical, chemical, and microbiological test characteristics), a retest period applicable to all future batches of the bulk drug substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification until the retest date.

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch to batch variability is small, it is advantageous to combine the data into one overall estimate and this can be done by first applying appropriate statistical tests (for example, p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period may depend on the minimum time a batch may be expected to remain within acceptable and justified limits.

The nature of any degradation relationship will generally determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted. Under the circumstances, it is normally unnecessary to go through the formal statistical analysis but merely to provide a full justification for the omission.

Limited extrapolation of the real time data beyond the observed range to extend expiration dating at approval time, particularly where the accelerated data support this, may be undertaken. However, this assumes that the same degradation relationship will continue to apply beyond the observed data and hence the use of extrapolation must be justified in each application in terms of what is known about the mechanism of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data, etc.

Any evaluation should cover not only the assay, but the levels of degradation products and other appropriate attributes.

Statements/Label ling

A storage temperature range may be used in accordance with relevant national/regional requirements. The range should be based on the stability evaluation of the drug substance. Where applicable, specific requirements should be stated, particularly for drug substances that cannot tolerate freezing. Terms such as ‘ambient conditions’ or ‘room temperature’ should not be used.

A re-test period should be derived from the stability information.

DRUG PRODUCT

General

The design of the stability programme for the finished product should be based on the knowledge of the behavior and properties of the drug substance and the experience gained from clinical formulation studies and from the stability studies on the drug substance. The likely changes on storage and the rationale for the selection of product variables to include in the testing programme should be stated.

Selection of Batches

Stability information from accelerated and long term testing should be provided on three batches of the same formulation and dosage form in the containers and closure proposed for marketing. If smaller packaging is used, it has to simulate the packaging actually proposed for marketing. Two of the three batches should be at least pilot scale. The third batch may be smaller. The long term testing should cover at least 6 months duration at the time of submission. The manufacturing process to be used should meaningfully simulate that which would be applied to large scale batches for marketing. The process should provide product of the same quality intended for marketing, and meeting the same quality specification as to be applied for release of material. Where possible, batches of the finished product should be manufactured using identifiably different batches of drug substance.

Data on laboratory scale batches should not be used as primary stability information. Data on associated formulations or packaging may be submitted as supportive information. The first three production batches manufactured post approval, if not submitted in the original Registration Application, should be placed on accelerated and long-term stability studies using the same stability protocols as in the approved drug application.

Test Procedures and Test Criteria

The testing should cover those features susceptible to change during storage and likely to influence quality, safety, and/or efficacy. Analytical test procedures should be fully validated and the assays should be stability-indicating. The need for the extent of replication should depend on the results of validation studies.

The range of testing should cover not only chemical and biological stability but also loss of preservative, physical properties and characteristics, organoleptic properties, and, where required, microbiological attributes. Preservative efficacy testing and assays on stored samples should be carried out to determine the content and efficacy of antimicrobial preservatives.

Specifications

Limits of acceptance should relate to the release limits (where applicable), to be derived from consideration of all the available stability information. The shelf life specification could allow acceptable and justifiable derivations from the release specification based on the stability evaluation and the changes

observed on storage. It should need to include specific upper limits for degradation products, the justification for which should be influenced by the levels observed in material used in pre-clinical studies and clinical trials. The justification for the limits proposed for certain other tests such as particle size and/or dissolution rate should include reference to the results observed for batch(es) used in bioavailability and/or clinical studies. Any differences between the release and shelf life specifications for antimicrobial preservatives should be supported by preservative efficacy testing.

Storage Test Conditions

The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use (e.g., reconstitution or dilution as recommended in the labelling).

See the Table below for accelerated and long term storage conditions and minimum times. An assurance that long term testing will continue to cover the expected shelf life should be provided.

Other storage conditions are allowable if justified. Heat sensitive drug products should be stored under an alternative lower temperature condition which will eventually become the designated long term storage temperature. Special consideration may need to be given to products which change physically or even chemically at lower storage conditions, e.g., suspensions or emulsions which may sediment or cream, oils, and semi-solid preparations which may show an increased viscosity. Where a lower temperature condition is used, the six months accelerated testing should be carried out at a temperature at least 15°C above its designated long term storage temperature (together with appropriate relative humidity conditions for that temperature). For example, for a product to be stored long term under refrigerated conditions, accelerated testing should be conducted at 25°C ± 2°C/60 percent RH ± 5 percent RH. The designated long term testing conditions will be reflected in the labelling and expiration date.

Storage under conditions of high relative humidities applies particularly to solid dosage forms. For products such as solutions, suspensions, etc., contained in packs designed to provide a permanent barrier to water loss, specific storage under conditions of high relative humidity is not necessary but the same range of temperatures should be applied. Low relative humidity (e.g., 10-20 percent RH) can adversely affect products packed in

semi-permeable containers (e. g., solutions in plastic bags) and consideration should be given to appropriate testing under such conditions.

	Conditions	Minimum time period at submission
Long term testing	250c ± 2°C/60% **RH** ± 5%	***6*** months
Accelerated testing	40°C ± 2°C/75% **RH** ± 5%	**6** months

Where 'significant change' occurs due to accelerated testing, additional testing at an intermediate condition, e.g., 30"C ± 2°C/60 percent ± 5 percent RH should be conducted. 'Significant change' at the accelerated condition is defined as:

1. A 5 percent potency loss from the initial assay value of a batch;

2. Any specified degradant exceeding its specification limit;

3. The product exceeding its pH limits;

4. Dissolution exceeding the specification limits for 12 capsules or tablets;

5. Failure to meet specifications for appearance and physical properties, e.g., color, phase separation, resuspendibility, delivery per actuation, caking, hardness, etc.

Should significant change occur at 40°C/75 percent RH then the initial Registration Application should include a minimum of 6 months data from an ongoing one year study at 30°C/60 percent RH; the same significant change criteria would then apply.

The long term testing should be continued for a sufficient time beyond 6 months to cover shelf life at appropriate test periods. The further accumulated data should be submitted to the authorities during the assessment period of the Registration Application.

The first three production batches manufactured post approval, if not submitted in the original Registration Application, should be placed on accelerated and long term stability studies using the same stability protocol as in the approved drug application.

Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the drug product. Testing should normally be every three months over the first year, every six months over the second year, and then annually.

The use of matrixing or bracketing maybe applied, if justified (see Glossary).

Packaging Materials

The testing should be carried out in the final packaging proposed for marketing. Additional testing of unprotected drug product can form a useful part of the stress testing and pack evaluation, as can studies carried out in other related packaging materials in supporting the definitive pack(s).

Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information which should cover, as necessary, physical, chemical, biological, and microbiological quality characteristics, including particular properties of the dosage form (for example, dissolution rate for oral solid dose forms).

The purpose of the stability study is to establish, usually based on testing a minimum of three batches of the drug product, a shelf-life and label storage instructions applicable to all future batches of the dosage form manufactured and packed under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification until the expiration date.

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95 % one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch to batch variability is small, it is advantageous to combine the data into one overall estimate and this can be done by first applying appropriate statistical tests (for example, p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life may depend on the minimum time a batch may be expected to remain within acceptable and justified limits.

The nature of the degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf-life will be granted, it is normally unnecessary to go through the formal statistical analysis but only to provide a justification for the omission.

Limited extrapolation of the real time data beyond the observed range to extend expiration dating at approval time, particularly where the accelerated data support this, may be undertaken. However, this assumes that the same degradation relationship will continue to apply beyond the observed data and hence the use of extrapolation should be justified in each application in terms of what is known about the mechanisms of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data, etc.

Any evaluation should consider not only the assay, but the levels of degradation products and appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance, different stability, and degradation performance.

The stability of the drug products after reconstituting or diluting according to labelling should be addressed to provide appropriate and supportive information.

Statements/Labelling

A storage temperature range may be used in accordance with relevant national/regional requirements. The range should be based on the stability evaluation of the drug product. Where applicable, specific requirements should be stated particularly for drug products that cannot tolerate freezing.

The terms such as ‘ambient conditions’ or ‘room temperature’ should not be used.

There should be a direct linkage between the label statement and the demonstrated stability characteristics of the drug product.

ANNEX 1

GLOSSARY AND INFORMATION

The following terms have been in general use and the following definitions are provided to facilitate interpretation of the guideline.

Accelerated Testing

Studies designed to increase the rate of chemical degradation or physical change of an active drug substance or drug product using exaggerated storage conditions as part of the formal, definitive, storage programme.

These data, in addition to long term stability studies, may also be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the impact of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Active Substance; Active Ingredient; Drug Substance; Medicinal Substance

The unformulated drug substance which may be subsequently formulated with excipients to produce the drug product.

Bracketing

The design of a stability schedule so that at any time point only the samples on the extremes, for example, of container size and/or dosage strengths, are tested. The design assumes that the stability of the intermediate condition samples is represented by those at the extremes.

Where a range of dosage strengths is to be tested, bracketing designs may be particularly applicable if the strengths are very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Where a range of sizes of immediate containers is to be evaluated, bracketing designs may be applicable if the material of composition of the container and the type of closure are the same throughout the range.

Climatic Zones

The concept of dividing the world into four zones based on defining the prevalent annual climatic conditions.

Dosage Form; Preparation

A pharmaceutical product type, for example, tablet, capsule, solution, cream, etc., that contains a drug ingredient generally, but not necessarily, in association with excipients.

Drug Product; Finished Product

The dosage form in the final immediate packaging intended for marketing.

Excipient

Anything other than the drug substance in the dosage form.

Expiry/Expiration Date

The date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions, and after which it must not be used.

Formal (Systematic) Studies

Formal studies are those undertaken to a proapproval stability protocol which embraces the principles of these guidelines.

Long Term (Real Time) Testing

Stability evaluation of the physical, chemical, biological, and microbiological characteristics of a drug product and a drug substance, covering the expected duration of the shelf life and re-test period, which are claimed in the submission and will appear on the labelling.

Mass Balance; Material Balance

The process of adding together the assay value and levels of degradation products to see how closely these add up to 100 percent of the initial value, with due consideration of the margin of analytical precision.

This concept is a useful scientific guide for evaluating data but it is not achievable in all circumstances. The focus may instead be on assuring the specificity of the assay, the completeness of the investigation of routes of degradation, and the use, if necessary, of identified degradants as indicators of the extent of degradation via particular mechanisms.

Matrixing

The statistical design of a stability schedule so that only a fraction of the total number of samples are tested at any specified sampling point. At a subsequent sampling point, different sets of samples of the total number would be tested. The design assumes that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container and closure, and, possibly, in some cases, different container/closure systems.

Matrixing can cover reduced testing when more than one variable is being evaluated. Thus the design of the matrix will be dictated by the factors needing to be covered and evaluated. This potential complexity precludes inclusion of specific details and examples, and it may be desirable to discuss design in advance with the Regulatory Authority, where this is possible. In every case it is essential that all batches are tested initially and at the end of the long term testing.

Mean Kinetic Temperature

When establishing the mean value of temperature, the formula of J. D. Haynes (J. *Pharm. Sci.,* 60:927-929, 1971) can be used to calculate the mean kinetic temperature. It is higher than the arithmetic mean temperature and takes into account the Arrhenius equation from which Haynes derived his formula.

New Molecular Entity; New Active Substance

A substance which has not previously been registered as a new drug substance with the national or regional authority concerned.

Pilot Plant Scale

The manufacture of either drug substance or drug product by a procedure fully representative of and simulating that to be applied on a full manufacturing scale.

For oral solid dosage forms this is generally taken to be a minimum scale of one tenth that of full production.

Primary Stability Data

Data on the drug substance stored in the proposed packaging under storage conditions that support the proposed re-test date.

Data on the drug product stored in the proposed container-closure for marketing under storage conditions that support the proposed shelf life.

Re-Test Date

The date when samples of the drug substance should be re-examined to ensure that material is still suitable for use.

Re-Test Period

The period of time during which the drug substance can be considered to remain within the specification and therefore acceptable for use in the manufacture of a given drug product, provided that it has been stored under the defined conditions; after this period, the batch should be retested for compliance with specification and then used immediately.

Shelf-Life; Expiration Dating Period

The time interval that a drug product is expected to remain within the approved shelf-life specification provided that it is stored under the conditions defined on the label in the proposed containers and closure.

Specification-Release

The combination of physical, chemical, biological, and microbiological test requirements that determine that a drug product is suitable for release at the time of its manufacture.

Specification-Check/Shelf-Life

The combination of physical, chemical, biological and microbiological test requirements that a drug substance should meet up to its retest date or a drug product should meet throughout its shelf life.

Storage Conditions Tolerances

The acceptable variation in temperature and relative humidity of storage facilities.

The equipment should be capable of controlling temperature to a range of ± 2°C and Relative Humidity to ± 5% RH. The actual temperatures and humidities should be monitored during stability storage. Short term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed by the applicant and reported if judged to impact stability results. Excursions that exceed these ranges (i.e., ± 2°C and/or& 5% RH) for more than 24 hours should be described in the study report and their impact assessed.

Stress Testing (Drug Substance)

These studies are undertaken to elucidate intrinsic stability characteristics. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated tests.

Stress testing is conducted to provide data on forced decomposition products and decomposition mechanisms for the drug substance. The severe conditions that may be encountered during distribution can be covered by stress testing of definitive batches of drug substance.

These studies should establish the inherent stability characteristics of the molecule, such as the degradation pathways, and lead to identification of degradation products and hence support the suitability of the proposed analytical procedures. The detailed nature of the studies will depend on the individual drug substance and type of drug product.

This testing is likely to be carried out on a single batch of material and to include the effect of temperatures in 10°C increments above the accelerated temperature test condition (e.g., 50°C, 60°C, etc.), humidity where appropriate (e.g., 75 percent or greater), oxidation and photolysis on the drug substance plus its susceptibility to hydrolysis across a wide range of pH values when in solution or suspension.

Results from these studies will form an integral part of the information provided to regulatory authorities.

Light testing should bean integral part of stress testing. (The standard conditions for light testing are considered in separate VICH guidelines.)

It is recognized that some degradation pathways can be complex and that under forcing conditions decomposition products may be observed which are unlikely to be formed under accelerated or long term testing. This information may be useful in developing and validating suitable analytical methods, but it may not always be necessary to examine specifically for all degradation products, if it has been demonstrated that in practice these are not formed.

Stress Testing (Drug Product)

Light testing should be an integral part of stress testing (see separate guidelines).

Special test conditions for specific products (e.g., metered dose inhalations and creams and emulsions) may require additional stress studies.

Supporting Stability Data

Data other than primary stability data, such as stability data on early synthetic route batches of drug substance, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, product presented in containers and/or closures other than those proposed for marketing, information regarding test results on containers, and other scientific rationale that support the analytical procedures, the proposed retest period or shelf life and storage conditions.

Footnote

This guideline has been developed within the Expert Working Group (Quality) of VICH.

Discussions are still being pursued within the Expert Working Group to define and standardize the conditions for light stability testing of active substances and dosages forms and the requirements for biological /biotechnological drug substances and products . These conditions are the subj ect of a separate document .

Attachment 1

Attachment to the Expert Working Group Minutes

On Tuesday September 30th, two issues pertaining to drug product 'significant change' remained to be resolved. The first issue involved the possible need for revision of the text to allow submission of the registration applications when unexpected failure occurs during the accelerated stability testing (40º±2ºC/75%± 5RH) portion of the stability studies. The second issue involved the possible need for revision of the text for item I under the definition for, drug product "significant change" as it pertains to microbiological assays.

It was agreed that the resolution of these two issues may largely be dealt with through incorporation of the expert Working Group interpretation of the language in the guidance document, as part of the meeting minutes rather than significantly changing the VICH language. The purpose of this approach is to establish an administrative record that will continue to be appropriately interpreted in the application of the guidance document to veterinary drug products.

For example, it was agreed that if an unexpected stability failure occurred at 3 months under accelerated stability conditions that intermediate stability testing would be initiated and the registration application could be submitted with 6 months long term data, 6 months accelerated stability testing data and 3 months intermediate stability testing data. Likewise, it was agreed that if an unexpected stability failure occurred at the 6 months accelerated testing period, then the sponsor would be expected to delay the submission of the registration application for 3 months while intermediate stability testing data was developed. In this instance, the registration application would contain 9 months long term stability testing 6 months accelerated stability testing data and 3 months intermediate testing data at the time of submission of the registration application.

It was further agreed that revision would not be made to the current VICH text but to suggest the following interpretation instead;

If a failure occurs during the accelerated stability study (40ºC/75%RH) which was not expected after the development studies, the Applicant could, after investigation of the failure and proper justification, submit a minimum of 3 months data at 30 °C/60% RH from an ongoing ***12*** month stability study.

The Expert Working Group also agreed that the text of item I under the definition for drug product ‘significant change’ as it pertains to microbiological assays did not need revision. Rather, the working group members felt that clarification of the interpretation of item I as it pertains to microbiological assays would be adequate. This clarification includes the understanding by the working group that “A 5 percent potency loss from the initial assay value of a batch” does not apply well as a significant change criteria for microbiological assays. The expert working group members agreed that when microbiological assays were being used that it would be acceptable to submit a justification for not meeting item I of the significant change criteria with the Registration Application. The working group agreed that when microbiological assays are used, the concept of the 5 percent potency loss might need some interpretation with regard to the precision of the assay